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EXAMINER	
NIKODEM,D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

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File

Office Action Summary	Applicati n No.	Applicant(s)	
	09/388,221	REED, JOHN	
	Examiner	Art Unit	
	David Nikodem	1633	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *12 May 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *10,12-17,19-26,28,30-37 and 39-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,18,27,29 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-9, 11, 18, 27-29 and 38 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the inventions of Groups II and X, and Groups VII and VIII, and Groups XI and XIII are not independent or distinct and that a search would not pose a serious burden on the examiner. Upon further review of the Groups set forth in the restriction requirement in Paper No. 6, the following groups have been rejoined: Groups II and X, and Groups VII and VIII, and Groups XI and XIII.

2. Furthermore, upon further review of claim 28, examiner has determined that this elected claim inadvertently has been placed within the wrong group. The claim is drawn to a method of detecting human NAC in a sample using an antibody according to claim 19. The claim was placed in Group I, drawn to NAC-associated nucleic acids, vectors, host cells, oligonucleotides and methods of expression, but should have been placed in group III, claims 19-22, 28, 40-43, and 52-54, drawn to anti-NAC antibodies and methods using such. Accordingly, and to expedite examination herein, claim 28 is removed from Group I and placed in Group III, as per the groups originally set forth.

3. Thus, claims 10, 12-17, 19-26, 28, 30-37, and 39-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the

restriction (election) requirement in Paper No. 9. Claims 1-65 are pending and claims 1-9, 11, 18, 27, 29 and 38 are examined in the instant office action.

4. Note that in view of the fact that claim 28 has been removed from Group I and placed in Group III, the instant restriction has not been made final. It is further noted for the record that the traversal filed on 5/12/00 of the restriction in the Official office action mailed 3/10/00 did not traverse the propriety of the restriction regarding claims 1-9, 11, 18, 27, 29 and 38 as being distinct and independent from the other claims.

Claim Objections

5. Claim 38 is objected to because of the following informalities: the language "modulating the level apoptosis" should read –modulating the level of apoptosis--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

7. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. In claim 3, the use of the language "substantially the same" is vague and indefinite with regard to the definition of "substantially." It is unclear from this language as to what DNA sequence constitutes "substantially the same" sequence to that in SEQ

ID Nos:1, 3 and 5. It is indefinite as to whether, for example, 40% identity between the two sequences is "substantially the same," or whether, for example, 80% is an appropriate cut-off limit to embrace the term "substantially the same." Appropriate correction is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

10. Claims 1-9, 11, 18, 27, 29 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding a NB-ARC and CARD containing protein (NAC) selected from DNA encoding SEQ ID Nos:2, 4 or 6, and/or wherein said nucleic acid encodes biologically active NAC that is degenerate with respect to SEQ ID Nos:2, 4 or 6, and/or wherein said nucleic acid hybridizes under high stringency to the NAC coding portion of any of SEQ ID Nos:1, 3 and 5, and/or wherein said nucleic acid is the same sequence as set forth in SEQ ID Nos:1, 3 or 5, and/or wherein said nucleic acid is a cDNA, and/or a vector and/or recombinant cells containing said nucleic acid, and/or oligonucleotides at least 15 nucleotides in length that hybridize to SEQ ID Nos:1, 3 and 5, and/or said oligonucleotide labeled with a detectable marker, and/or a method for expressing NAC using said recombinant cells, and/or a method of identifying nucleic acids encoding a mammalian NAC using said oligonucleotides that hybridize under high stringency conditions, and/or single stranded DNA primers derived from nucleic acid sequences

set forth in SEQ ID Nos:1, 3 and 5, and/or a method for modulating the level of apoptosis in a cell comprising introducing a NAC nucleic acid molecule into a cell and expressing said NAC in said cell, wherein said NAC modulates apoptosis, *in vitro*, **does not reasonably provide enablement for** a functional fragment of an isolated nucleic acid encoding NAC selected from DNA encoding SEQ ID Nos:2, 4 or 6, and/or further claim limitations set forth upon said functional fragment of said isolated nucleic acid, and/or DNA that hybridizes under moderately stringent conditions to an isolated nucleic acid encoding NAC selected from DNA encoding SEQ ID Nos:2, 4 or 6 and/or a method of modulating the level of apoptosis in a cell comprising introducing a nucleic acid molecule encoding any NAC, *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

11. The claims are drawn to an isolated nucleic acid encoding a NB-ARC and CARD containing protein (NAC) selected from DNA encoding SEQ ID Nos:2, 4 or 6, and/or wherein said nucleic acid encodes biologically active NAC that is degenerate with respect to SEQ ID Nos:2, 4 or 6, and/or a DNA that hybridizes under moderately stringent conditions to said isolated nucleic acid. The claims are further drawn to limitations on this base claim wherein said nucleic acid hybridizes under high stringency to the NAC coding portion of any of SEQ ID Nos:1, 3 and 5, and/or wherein said nucleic acid is the same sequence as set forth in SEQ ID Nos:1, 3 or 5, and/or wherein said nucleic acid is a cDNA, and/or a vector and/or recombinant cells containing said nucleic acid, and/or oligonucleotides at least 15 nucleotides in length that hybridize to SEQ ID

Nos:1, 3 and 5, and/or said oligonucleotide labeled with a detectable marker (and kits thereof), and/or a method for expressing NAC using said recombinant cells, and/or a method of identifying nucleic acids encoding a mammalian NAC using said oligonucleotides that hybridize under high stringency conditions, and/or single stranded DNA primers derived from nucleic acid sequences set forth in SEQ ID Nos:1, 3 and 5, and/or a method for modulating the level of apoptosis in a cell comprising introducing a NAC encoding nucleic acid molecule as set forth in SEQ ID Nos:1, 3 and 5, into a cell and expressing said NAC in said cell, wherein said NAC modulates apoptosis.

12. The specification teaches the DNA of SEQ ID Nos:1, 3 and 5 and that said sequences encode NAC proteins of SEQ ID Nos:2, 4 and 6. The specification further teaches (see examples 1-3) the isolation of said DNAs, construction of expression vectors and the expression and isolation of said proteins. The specification further teaches (examples 3-6) the partial characterization of said NAC proteins. The specification defines (page 32) moderately stringent hybridization conditions, but fails to teach DNA and/or oligonucleotides that hybridize under these conditions. The specification further fails to teach **any** fragments of **any** of the NAC proteins of SEQ ID Nos:2, 4 and 6.

13. Firstly, the moderately stringent hybridization conditions set forth in the specification (page 32) of 50% formamide, 5X Denhart's solution, 5X SPEE, 0.2% SDS at 42°C, followed by a wash in 0.2X SPEE, 0.2% SDS at 65°C, would allow for the binding of numerous DNAs and/or oligonucleotides. The specification states (page 32) that the conditions would permit nucleic acid molecules of 60% identity to hybridize to

the NAC DNA set forth in SEQ ID Nos:1, 3 and 5. It is widely known in the art that DNAs that are less than 100% identical, may not encode the same protein and that the art of hybridization between two DNA molecules results in non-specific binding, depending on the length of DNA and the hybridization conditions used. Therefore, a population of hybridizing DNAs that are 60% or even 90% identical to NAC will be nonspecific DNAs that encode molecules of unknown function – proteins that do not have NAC activity and/or are not related to NAC. The specification does not provide any guidance for one of skill in the art to determine the function of these non-NAC encoding DNAs. As a result, it would require undue trial and error experimentation to determine the function of each of the potentially thousands of DNAs that hybridize under said moderately stringent conditions. The amount of experimentation would require the screening of all the hybridized DNAs for NAC function.

14. Secondly, the claims are drawn to functional fragments of NAC. It is well known in the art that the open reading frame of a protein contains certain domains that confer protein activity, e.g. enzymatic, binding, *etc.*. Such a region may be as small as ten amino acids or a stretch as large as, for example, 1000 amino acids. However, the alteration of one amino acid can result in an inactive protein. The specification teaches the open reading frame (ORF) of NAC, as set forth in SEQ ID Nos:2, 4 and 6. The specification lacks any guidance for one of skill in the art to determine what region or fragment of said ORF is responsible for biological NAC activity. The specification fails to teach any functional fragment of the ORF of NAC. In view of this lack of guidance,

one of skill in the art would be unable to determine, without undue experimentation, what fragments of NAC are functional fragments.

15. For example, even one amino acid substitutions may result in altered protein phenotype and/or function. At the time of filing and subsequently thereafter, the state of the art pertaining to modifications embracing amino acid substitutions, deletions, inversions, etc. of a polypeptide is unpredictable with regard to retaining the phenotype of the polypeptide or protein. Ding *et al.* teaches in the abstract of the reference that a single conservative amino acid substitution of alanine with isoleucine in IL-10 converts the protein to a molecule with immunostimulatory activity and that "this single conservative residue alteration significantly affects ligand affinity for receptor."

16. Therefore, it is unpredictable for one skilled in the art to determine what amino acid regions, or fragments, of NAC retain functional activity. For example, a fragment of one less amino acid on either the 5` or 3` terminus may result in an inactive protein. It would require undue experimentation to determine the regions of NAC that retain NAC activity. The amount of experimentation required would include the trial and error testing of a series of fragments that span SEQ ID Nos:2, 4 and 6 to determine whether or not NAC function is present. It would require the generation of DNA encoding said fragments, polypeptide expression and characterization to determine whether or not NAC activity of the polypeptide are retained. Thus, the invention is not enabled over the full scope as claimed.

17. Thirdly, the method claim drawn to modulating the level of apoptosis in a cell reads on a cell *in vivo*. Said claim is broadly drawn and does not recite a context, with

regard to use *in vivo* or use *in vitro*, thus reading on both, *in vivo* and *in vitro*. It is well known that the state of the art of *in vivo* delivery of nucleic acids and gene therapy is unpredictable. The specification fails to provide guidance to the skilled artisan on the parameters for gene delivery for the breadth of the claimed invention, namely on *in vivo* use. Eck, *et al.* teaches that numerous factors complicate the gene therapy and the *in vivo* nucleic acid delivery arts which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced.

18. No general guidelines existed at the time of filing or at present for gene therapy and/or delivery of nucleic acids *in vivo*. The quantity of experimentation required to practice the invention as claimed would require de novo trial and error experimentation to define specific parameters and protocols necessary for in vivo success.

19. Therefore, it would require undue experimentation to practice the invention over the full scope as claimed and thus the invention is not enabled as claimed.

20. Claims 1-9, 11, 18, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims have been described in paragraph 11 of the instant office action. The essential element of the claim is DNA that hybridizes to SEQ ID Nos:1, 3 and 5 under the disclosed moderately stringent conditions. The specification fails to provide **any** evidence of **any** DNA that hybridizes to NAC DNA of said SEQ ID Nos. As previously described, it is well known in the art that DNA hybridization under moderately stringent conditions will result in a large degree of non-specific hybridization and that many of these DNAs will not encode proteins of NAC function. Thus, a person of skill in the art would expect substantial variation among species encompassed within the scope of the claims because the moderately stringent conditions set forth allow for the hybridization of unknown molecules. Thus, a large number of DNAs of unknown function will hybridize under the disclosed conditions. In view of such, it is unclear that applicants have provided a representative number of species to describe the broad genus of hybridizing DNAs and therefore, applicants are not in possession of the invention as claimed.

22. Further, the claims are broadly drawn to functional fragments of the isolated nucleic acid encoding NAC, as selected from DNA encoding the proteins of SEQ ID Nos:2, 4 and 6 and/or DNA degenerate to said DNA that encodes biologically active NAC. As previously described, biological activity of a protein is limited to certain

regions, or domains, of the protein. The specification provides guidance to make and/or use only the full length ORF. The specification does not provide any teachings on how to make and/or use any protein fragments of the ORF of SEQ ID Nos:2, 4 and 6. The embodiment of one species (the full length ORF) of biologically active NAC does not embrace the broad genus of all proteins and/or fragments there of that have biological NAC activity. It is unclear that applicants have provided a representative number of species of proteins and/or fragments thereof to describe the genus. In view of such, applicants were not in possession of the invention as claimed.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 2, 8, 9, 11, 27 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Nagase, *et al.*.

25. The claims have been described in paragraph 10 of the instant office action. The claims read broadly on any nucleic acid molecules that hybridize to the DNA of SEQ ID Nos:1, 3 and 5 under stringent conditions, and on oligonucleotides of 15 bp or greater that hybridize to the DNA of SEQ ID Nos:1, 3 and 5. It is well known in the art that as the level of identity between hybridized DNA increases, a stronger degree of

hybridization results. Therefore, DNA stretches that have 100% identity will hybridize with high affinity and thus will hybridize under high stringency conditions.

26. The reference teaches (see Office Sequence Search, Result 1 of searches us-09-388-221-1.rge, us-09-388-221-3.rge and us-09-388-221-5.rge) nucleic acids of 100% identity to SEQ ID Nos:1, 3 and 5. For SEQ ID NO:1, a continuous nucleic acid of 3,780 bp is identified, for SEQ ID NO:3 a continuous nucleic acid of 2879 bp is identified and for SEQ ID NO:5 a continuous nucleic acid of 2879 is identified. In view of such, the reference clearly anticipates nucleic acids, oligonucleotides and kits using said oligonucleotides, that are of at least 15 bp in length and that hybridize to SEQ ID Nos:1, 3 and 5.

27. Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by Seshagiri, *et al.*.

28. The claims have been described in paragraph 10 of the instant office action. Briefly, the claim is broadly drawn to a method of apoptosis in a cells comprising introducing any nucleic acid molecule encoding NAC and expressing NAC in said cell. The specification teaches (page 84) that "the NAC of the invention interacts with other NB-ARC and CARD-containing proteins, Apaf-1 and CED-4."

29. The reference teaches (abstract) that cells transfected with DNA that encodes CED-4 and that co-express CED-4 and CED-3 stimulated the induction of apoptosis, *in vitro*. The reference further teaches (page 455) that CED-4 is required for programmed cell death. In view of such, the reference teaches that cells transfected with DNA that

encodes CED-4 and subsequently expresses CED-4, a NAC, modulates the level of apoptosis. In view of such, the reference clearly anticipates the broadly drawn claim.

30. A search of the prior art of record against SEQ ID NOS:1-6 revealed homology of 93.8, 80.3, 97.6, 78.5, 91.4 and 79.6, respectively (all from Nagase, *et al.* and Koehrer, *et al.* (EMBL:AL117470)). However, except for the oligonucleotides and hybridizing DNA, the art does not anticipate the claimed SEQ ID NOS. claimed because it does not have 100% identity.

31. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Nikodem whose telephone number is (703) 308-8361. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3230 for regular communications and (703) 305-3230 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

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July 27, 2000

JOHN L. LeGUYADER
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